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(54) DOSAGE FORMS FOR AMELIORATING MALE ERECTILE DYSFUNCTION

ANWENDUNGSFORMEN ZUR BEHANDLUNG DER MÄNNLICHEN EREKTILEN DYSFUNKTION

FORMES PHARMACEUTIQUES DESTINEES A AMELIORER LES DYSERECTIONS CHEZ L'HOMME

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WO-A-95/20377	**WO-A-95/28930**
WO-A-96/41619	**WO-A-97/06786**
GB-A- 1 548 022	**US-A- 3 928 566**
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- **DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US ACCESSION NR. 95159287, XP002063017 & J. P. HEATON ET AL.: "RECOVERY OF ERECTILE FUNCTION BY THE ORAL ADMINISTRATION OF APOMORPHINE" UROLOGY, vol. 45, no. 2, 1995, pages 200-206,**

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Description

[0001] This invention relates to the manufacture of dosage forms for ameliorating erectile dysfunction in male patients. More particularly, this invention relates to the manufacture of fast-dispersing dosage forms of drugs for amelioration of erectile dysfunction in male patients.

[0002] A normal erection occurs as a result of a coordinated vascular event in the penis. This is usually triggered neurally and consists of vasodilatation and smooth muscle relaxation in the penis and its supplying arterial vessels. Arterial inflow causes enlargement of the substance of the corpora cavernosa. Venous outflow is trapped by this enlargement, permitting sustained high blood pressures in the penis sufficient to cause rigidity. Muscles in the perineum also assist in creating and maintaining penile rigidity. Erection may be induced centrally in the nervous system by sexual thoughts or fantasy, and is usually reinforced locally by reflex mechanisms.

[0003] Male erectile dysfunction (MED) is defined as the inability to achieve and sustain an erection sufficient for intercourse. In any given case this can result from psychological disturbances (psychogenic), from physiological abnormalities in general (organic), from neurological disturbances (neurogenic), hormonal deficiencies (endocrine) or from a combination of the foregoing.

[0004] The effect of apomorphine on penile tumescence in male patients has been studied. These studies show that while apomorphine can indeed induce an erection in a psychogenic male patient, the apomorphine dose required to achieve a significant erectile response is usually accompanied by nausea or other serious undesirable side effects such as hypertension, flushing and diaphoresis. The specific mechanisms by which apomorphine acts to produce an erectile response in a human patient are not yet completely understood, however.

[0005] Moreover, apomorphine has been shown to have very poor oral bioavailability. See, for example, Baldessarini et al., in Gessa et al., eds., Apomorphine and Other Dopaminomimetics, Basic Pharmacology, Vol. 1, Raven Press, N.Y. (1981), pp. 219-228.

[0006] WO95/28930 discloses sublingual apomorphine dosage forms, usually containing about 2.5 to about 10 milligrams of apomorphine, and dissolving in water within a time period of at least about 2 minutes but less than about 10 minutes, preferably about 3 minutes to about 5 minutes, have been found to be effective in male patients suffering from psychogenic erectile dysfunction for the induction and maintenance of an erection sufficient for intercourse (i.e. vaginal penetration) without nausea or other undesirable side effects. The apomorphine is administered sublingually, preferably about 15 to 20 minutes prior to sexual activity, and so as to maintain a predetermined circulating serum levels and mid-brain tissue levels of apomorphine during the period of sexual activity.

[0007] The foregoing sublingual apomorphine dosage forms are also suitable for screening patients complaining of erectile dysfunction so as to identify patients of psychogenic etiology.

[0008] PCT/GB96/02020 discloses a pharmaceutical composition for oral administration comprising a carrier and, as active ingredient, a dopamine agonist, in which the composition is in the form of a fast-dispersing dosage form designed to release the active ingredient rapidly in the oral cavity.

[0009] It was found that such fast-dispersing dosage forms promote pre-gastric absorption of the active ingredient, that is, absorption of the active ingredient from that part of the alimentary canal prior to the stomach. The term "pre-gastric absorption" thus includes buccal, sublingual, oropharyngeal and oesophageal absorption. Dopamine agonists absorbed by such pre-gastric absorption pass straight into the systemic circulatory system thereby avoiding first pass metabolism in the liver. Accordingly, bioavailability of dopamine agonists absorbed in this way may also be increased. This means that the dose of such dopamine agonists may be reduced whilst still producing the desired beneficial effects and this decrease in dose will result in a corresponding reduction of unwanted side effects.

[0010] The pharmaceutical compositions disclosed in PCT/GB96/02020 were developed for the treatment and/or evaluation of Parkinson's disease.

[0011] US-A-5135752 discloses a matrix for a buccal dosage form which melts in the oral cavity at body temperature, but will not spontaneously deform at higher temperatures encountered in shipment and storage comprising 75 to 90% low MW polyethylene glycol, 0 to 4% medium to high MW polyethylene glycol, 0 to 4% long chain saturated carboxylic acid, 0.1 to 4% polyethylene oxide (MW 100,000 to 5,000,000) and 10 to 20% colloidal silica. Examples 2 and 3 disclose buccal tablets containing methyltestosterone which dissolved in the buccal space of volunteers over a period of from 3 to 12 minutes.

[0012] US-A-4877774 discloses tablets which can be administered by contact with the mucosa comprising crystalline complexes of steroid hormones with gamma-cyclodextrin. When administered sublingually the full dissolution of the tablets occurred over a period of from 10 to 15 minutes.

[0013] It has now been found that fast-dispersing dosage forms containing a dopamine agonist, such as apomorphine, may be used to treat male erectile dysfunction.

[0014] According to the present invention there is provided the use of a pharmaceutical composition for oral administration comprising a carrier and active ingredient selected from a dopamine agonist, testosterone and mixtures thereof, the composition being in the form of a solid fast-dispersing dosage form which disintegrates within 1 to 60 seconds

of being placed in the oral cavity for the manufacture of a medicament for treatment of male erectile dysfunction.

[0015] The use of a solid fast-dispersing dosage form has several advantages over the use of conventional sublingual tablets.

[0016] The efficiency of the fast-dispersing dosage form allows low doses to be employed thereby reducing undesirable side effects, particularly nausea and vomiting.

[0017] The dosage form acts more quickly than sublingual tablets which allows the dose to be taken when it is required rather than a considerable time before sexual activity. This is both psychologically and socially preferable to sucking a tablet for several minutes in advance of sexual activity.

[0018] There is a faster offset of action since the active ingredient is rapidly absorbed rather than absorbed over a prolonged period of time. The faster offset avoids painful persistent erection.

[0019] The rapid onset and offset of action is less likely to induce tolerance to the dopamine agonist.

[0020] One example of a fast-dispersing dosage form is described in U.S. Patent No. 4855326 in which a melt spinnable carrier agent, such as sugar, is combined with an active ingredient and the resulting mixture spun into a "candy-floss" preparation. The spun "candy-floss" product is then compressed into a rapidly dispersing, highly porous solid dosage form.

[0021] U.S. Patent No. 5120549 discloses a fast-dispersing matrix system which is prepared by first solidifying a matrix-forming system dispersed in a first solvent and subsequently contacting the solidified matrix with a second solvent that is substantially miscible with the first solvent at a temperature lower than the solidification point of the first solvent, the matrix-forming elements and active ingredient being substantially insoluble in the second solvent, whereby the first solvent is substantially removed resulting in a fast-dispersing matrix.

[0022] U.S. Patent No. 5079018 discloses a fast-dispersing dosage form which comprises a porous skeletal structure of a water soluble, hydratable gel or foam forming material that has been hydrated with water, rigidified in the hydrated state with a rigidifying agent and dehydrated with a liquid organic solvent at a temperature of about 0°C or below to leave spaces in place of hydration liquid.

[0023] Published International Application No. WO 93/12769 (PCT/JP93/01631) describes fast-dispersing dosage forms of very low density formed by gelling, with agar, aqueous systems containing the matrix-forming elements and active ingredient, and then removing water by forced air or vacuum drying.

[0024] U.S. Patent No. 5298261 discloses fast-dispersing dosage forms which comprise a partially collapsed matrix network that has been vacuum-dried above the collapse temperature of the matrix. However, the matrix is preferably at least partially dried below the equilibrium freezing point of the matrix.

[0025] Published International Application No. WO 91/04757 (PCT/US90/05206) discloses fast-dispersing dosage forms which contain an effervescent disintegration agent designed to effervesce on contact with saliva to provide rapid disintegration of the dosage form and dispersion of the active ingredient in the oral cavity.

[0026] U.S. Patent No. 5,595,761 discloses a particulate support matrix for use in making a rapidly dissolving tablet, comprising:

a first polypeptide component having a net charge when in solution, e.g. non-hydrolysed gelatin;
a second polypeptide component having a net charge of the same sign as the net charge of the first polypeptide component when in solution e.g. hydrolysed gelatin; and
a bulking agent, and wherein the first polypeptide component and the second polypeptide component together comprise about 2% to 20% by weight of the particulate support matrix and wherein the bulking agent comprises about 60% to 96% by weight of the particulate support matrix; and
wherein the second polypeptide component has a solubility in aqueous solution greater than that of the first polypeptide component and wherein the mass : mass ratio of the first polypeptide component to the second polypeptide component is from about 1 : ½ to about 1 : 14; and
wherein when the support matrix is introduced into an aqueous environment the support matrix is disintegrable within less than about 20 seconds.

[0027] The term "fast-dispersing dosage form" therefore encompasses all the types of dosage form described in the preceding paragraphs. However, it is particularly preferred that the fast-dispersing dosage form is of the type described in U.K. Patent No. 1548022, that is, a solid fast-dispersing dosage form comprising a network of the active ingredient and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

[0028] The composition of the invention disintegrates within 1 to 60 seconds, more preferably 1 to 30 seconds, especially 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.

[0029] In the case of the preferred type of fast-dispersing dosage form described above, the composition will preferably contain, in addition to the active ingredient, matrix forming agents and secondary components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

[0030] Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

[0031] One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension. This is especially helpful in the case of active agents that are not sufficiently soluble in water and must, therefore, be suspended rather than dissolved.

[0032] Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring agents include red, black and yellow iron oxides and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 available from Ellis & Everard. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame, acesulfame K and thaumatin. Suitable taste-masking agents include sodium bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

[0033] It is preferred that the dopamine agonist is selected from 5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline-10,11-diol(apomorphine),5,6,6a,7-tetrahydro-6-propyl-4H-dibenzo[de,g]quinoline-10,11-diol (N-propylnoraporphine), (5'α)-2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione(bromocriptine), 1-[(6-allylergolin-8β-yl) carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea (cabergoline), N'-[(8α)-9,10-didehydro-6-methylergolin-8-yl]-N,N-diethylurea (lisuride), [[(8β)-1,6-dimethylergolin-8-yl]methyl]-carbamic acid phenylmethyl ester (metergoline), (4aR)-trans-3,4,4a,5,6,10b-hexahydro-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol(naxagolide), 8-[(methylthio)methyl]-6-propylergoline(pergolide), 2-[4-(1,3-benzodioxol-5-ylmethyl)-1-piperazinyl]pyrimidine (tipepidil), 4-[2-(dipropylamino)ethyl]indolin-2-one (ropinirole), N,N-diethyl-N'-[(8α)-6-methylergolin-8-yl]urea (terguride) and (±)-N,N-diethyl-N'-[(3R,4aR*,10aS*)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[g]quinolin-3-yl]sulphamide (quinagolide) salts thereof and mixtures thereof. More preferably, the dopamine agonist is apomorphine or a salt, preferably an acid-addition salt, thereof, especially the hydrochloride salt.

[0034] It is also preferred that the dopamine agonist is present in the composition in an amount from 0.05 to 10mg, preferably 0.05 to 5mg.

[0035] The ability of dopamine receptor agonists to cause penile erections in rodents has been reported in a review by Lal (Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 1988, vol 12, pp. 117-164). It has been said that dose, and presumably plasma concentration, is critical with low doses of apomorphine or bromocriptine more effective than higher doses. It has been postulated that the physiological response is mediated through activation of central D2 receptors, since it has been shown that domperidone, a peripheral dopamine antagonist, does not interfere with this response. It is thus believed that plasma levels of apomorphine which induce dopamine receptor stimulation in Parkinsonian patients should also be effective in the treatment of male erectile dysfunction. However, the adverse side-effects, seen with apomorphine, of nausea, hypotension and sedation should be minimised by the use of as low a dose as possible.

[0036] Heaton et al, (1995), Urology, 45 : 200-206 reports patients with MED were given apomorphine liquid sublingually (doses of 10mg and 20mg), a sub-lingual tablet (5mg) or a slow-dissolving sub-lingual tablet (3mg and 4mg). Plasma levels were not recorded, but all doses and dosage forms were active, although side effects were a problem in some groups.

[0037] Van Laar et al, 1996, Movement Disorders, 11: 634-638 reported peak plasma levels after administration of sub-lingual apomorphine tablets (10mg). The peak plasma levels (ng/ml) were 7.0 ± 0.8 in one experiment and 7.4 ± 1.0 in another. In a third experiment, the sub-lingual tablets were acidified with ascorbic acid - the plasma level reduced slightly to 4.3 ± 1.5.

[0038] Since efficacy in the Heaton et al paper was seen with doses as low as 3mg, the peak plasma level to achieve this (based on dose-corrected data from the van Laar paper) would be around 1.3 to 2.2ng/ml.

[0039] A study on the therapeutic window of apomorphine in 3 groups of Parkinsonian patients, by the use of stepwise administration of apomorphine by intravenous infusion, demonstrated that it is possible to separate the onset of pharmacological activity and side-effects. Clinical efficacy, in the treatment of symptoms of Parkinson's disease, was seen at mean serum apomorphine levels above 3.8-5.0ng/ml whilst adverse effects were seen at mean serum apomorphine levels above 12.2-18.5ng/ml.

[0040] These reports would suggest that treatment of MED with apomorphine should generally aim for plasma levels

of at least 1 to 5 ng/ml and should not be allowed to exceed 10ng/ml.

[0041] The precise quantity of active ingredient will depend on the dopamine agonist chosen. Typical dose ranges for the dopamine agonists mentioned above are as follows:-

Apomorphine	1-20mg, preferably 1-10mg
N-propylnoraporphine	1-20mg, preferably 1-10mg
Bromocriptine	0.5-10mg, preferably 0.5-5mg
Cabergoline	0.05-2mg, preferably 0.05-0.5mg
Lisuride	0.05-2mg, preferably 0.05-0.4mg
Metergoline	4-20mg, preferably 4-8mg
Naxagolide	0.1-10mg, preferably 0.1-5mg
Pergolide	0.05-1mg, preferably 0.05-0.5mg
Piribedil	1-20mg, preferably 1-10mg
Ropinirole	0.25-20mg, preferably 0.25-5mg
Terguride	1-10mg, preferably 1-5mg
Quinagolide	0.1-5mg, preferably 0.1-1mg

[0042] Dopamine agonists may produce side effects such as nausea and vomiting. The composition used in the invention may be administered in conjunction with an anti-emetic. The anti-emetic may be conveniently administered in the same composition as the dopamine agonist.

[0043] Alternatively, the anti-emetic may be administered separately from the dopamine agonist by any of the usual oral or parenteral routes of administration, for instance, by tablets, capsules, suspensions, suppositories, infusions, injections, etc., at a suitable time which may be before, after or simultaneously with administration of the dopamine agonist. It is particularly preferred that the anti-emetic is formulated in a fast-dispersing dosage form of the type described above as it is envisaged that such a fast-dispersing dosage form of the anti-emetic would have many of the advantages associated with such formulations, such as increased bioavailability, dose reduction, ease of administration etc. as described above, although the precise advantages observed will depend on the nature of the anti-emetic chosen.

[0044] It is preferred that the anti-emetic is present in the composition in an amount of from 1 to 60mg. However, the precise quantity of anti-emetic to be administered to the patient will depend on the anti-emetic that is selected. Suitable anti-emetics include anti-histamines, such as trimethobenzamide; peripheral dopamine antagonists, such as 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one(domperidone) and salts thereof, and serotonin ($5\text{-}HT_3$)receptor antagonists, such as endo-1-methyl-N-(9-methyl-9-azabicyclo [3.3.1]non-3-yl)-1H-indazole-3-carboxamide(granisetron), 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one (ondansetron) and 1αH, 5αH-tropan-3α-yl indole-3-carboxylate (tropisetron) and salts thereof. Of these, domperidone is especially preferred.

[0045] Typical dose ranges for the anti-emetics mentioned above are as follows:-

Domperidone	20-120mg, preferably 30-60mg
Granisetron	1-10mg, preferably 1-3mg
Ondansetron	4-32mg, preferably 4-8mg
Tropisetron	1-10mg, preferably 1-5mg
N-[p[2-(dimethylamino)-ethoxy]benzyl]-3,4,5, trimethoxybenzamide	750-1000mg

[0046] Apomorphine is an opium alkaloid. Thus, as mentioned above, when apomorphine or another opium alkaloid or synthetic derivative is selected as the dopamine agonist, further side-effects, such as sedation, respiratory depression, hypotension, bradycardia, sweating and yawning may be produced. However, it has been found that all these side-effects can be treated by administration of an opioid antagonist in conjunction with the opioid dopamine agonist. The opioid antagonist may be conveniently administered in the same composition as the dopamine agonist. Thus, such a composition may also include an anti-emetic in addition to the dopamine agonist and opioid antagonist although this is not essential since the opioid antagonist also counteracts some of the emetic effects of the dopamine agonist. Alternatively, the opioid antagonist may be administered separately from the dopamine agonist by any of the usual oral or parenteral routes of administration at a suitable time which may be before, after or simultaneously with administration of the dopamine agonist. It is particularly preferred that the opioid antagonist is formulated in a fast-dispersing dosage form of the type described above as it is envisaged that such a fast-dispersing dosage form of the opioid antagonist would exhibit many of the advantages associated with such formulations, such as increased bioavailability, dose reduction, ease of administration etc. as described above, although the precise advantages observed will depend on the nature of the opioid antagonist chosen.

[0047] It is preferred that the opioid antagonist is present in the composition in an amount of from 0.5 to 100mg, more preferably 0.5 to 50mg. However, the precise quantity of opioid antagonist to be administered to the patient will depend on the opioid antagonist that is chosen. Suitable opioid antagonists include 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one(naloxone) and 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one (naltrexone) and salts, particularly acid-addition salts and, especially, the hydrochloride, thereof. A typical dose range for naloxone is 0.25-10mg, and for naltrexone is 10-100mg.

[0048] Alteration in endocrine function represents about one third of the total organic causes of male erectile dysfunction as reported in Aversa A et al, 1995, Mol Androl 7, 3-4. The administration of testosterone in the fast-dispersing dosage form assists in ameliorating this condition. A typical dosage range for oral administration of testosterone is 10 to 100mg, preferably 10 to 50mg. The composition may contain testosterone alone or in combination with a dopamine agonist.

[0049] The invention is further illustrated by the following Examples.

Example 1

Preparation of a fast-dispersing dosage form of apomorphine

(a) Preparation of apomorphine hydrochloride 2.0% dispersion

[0050] Gelatin (792g) and mannitol (594g) were dispersed in a portion of purified water (16kg) by mixing thoroughly in the bowl of a vacuum mixer. The mix was then heated to 40°C ± 2°C and homogenised for ten minutes. The mix was cooled down to room temperature (20-24°C). When cooled the apomorphine hydrochloride (360g) was added. The mix was homogenised to ensure dissolution of the drug. Citric acid (166.32g) was added gradually with stirring, to adjust the solution pH to 3.0. The remaining water (87.68g) was added to the mixer and the bulk mix homogenised to ensure dissolution was complete.

(b) Preparation of apomorphine hydrochloride 10mg units

[0051] 500mg of the apomorphine hydrochloride 2.0% dispersion formed in (a) above was dosed into each one of a series of pre-formed blister pockets having a pocket diameter of 16mm. The blister laminate comprised 200µm PVC coated with 40g per square metre PVdC. The product was frozen immediately in a liquid nitrogen freeze tunnel. The frozen product was then stored below -20°C for a minimum of 12 hours prior to freeze-drying in a freeze drier using a drying temperature of +10°C and a chamber pressure of 0.5mbar. The freeze dried units were then inspected for the presence of critical defects and the remainder of the batch sealed with lidding foil consisting of a paper/foil laminate (20µm aluminium). Each blister was then coded with a batch number and overwrapped in a preformed sachet by placing the blister in the sachet and sealing the open end of the sachet completely. Each sachet was then labelled with the product name, batch number, date of manufacture and suppliers name.

Each dosage unit had the following composition:

Ingredient	Parts by Weight	% by weight of composition
Purified water USP/EP*	446.880	89.4
Apomorphine HCl BP/EP	10.000	2.0
Gelatin EP/USNF	22.000	4.4
Mannitol EP/USP	16.500	3.3
Citric Acid EP/USP	4.620	0.9
Total (pH = 3)	500.000	100.0

* Signifies removed during the lyophilisation process.

Example 2

[0052] The following formulation was prepared using the process described in Example 1.

Ingredient	Parts by Weight	% by weight of composition
Purified water EP/USP*	433.000	86.60
Apomorphine HCl BP/EP	10.000	2.0
Gelatin EP/USNF	25.000	5.0
Mannitol EP/USP	20.000	4.0
Glycine USP	10.000	2.0
Citric Acid EP/USP	2.000	0.40
Total (pH = 4)	500.000	100.00

* signifies removed during lyophilisation process.

Example 3

Comparative pharmacokinetic study

[0053] The objective of this study was to compare the bioavailability of different fast dispersing formulations of apomorphine hydrochloride, prepared by the method of Example 1, following administration to six healthy volunteers.
[0054] Due to the emetic properties of apomorphine, subjects were pre-treated with the anti-emetic domperidone. Following two days of domperidone pre-treatment, subjects were randomised to receive the following apomorphine treatments:

10mg Apomorphine HCl (one unit of Example 1)
10mg Apomorphine HCl (one unit of Example 2)

[0055] Blood samples for pharmacokinetic analysis were taken pre-dose and at intervals for six hours after each dose of apomorphine. The results are reported in Figure 1 of the accompanying drawings. It will be seen that apomorphine is rapidly absorbed from both formulations of the fast-dispersing dosage form, reaching a maximum concentration in plasma after about 30 minutes.
[0056] The following examples further exemplify formulations which can be prepared using the process described in Example 1:

Example 4

[0057]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	438.500	87.70
Apomorphine HCl BP/EP	10.000	2.00
Gelatin EP/USNF	25.000	5.00
Mannitol EP/USP	20.000	4.00
Citric Acid EP/USP	1.500	0.30
Aspartame EP/USNF	2.500	0.50
Peppermint Flavour	2.500	0.50
Total	500.000	100.00

* signifies removed during lyophilisation process.

Example 5

[0058]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	215.000	86.00
Apomorphine HCl BP/EP	10.000	4.00
Gelatin EP/USNF	11.500	4.60
Mannitol EP/USP	10.000	4.00
Citric Acid EP/USP	1.500	0.60
Aspartame EP/USNF	2.000	0.80
Total	250.000	100.00

* signifies removed during lyophilisation process.

Example 6

[0059]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	441.000	88.20
Apomorphine HCl BP/EP	10.000	2.00
Gelatin EP/USNF	25.000	5.00
Mannitol EP/USP	20.000	4.00
Citric Acid EP/USP	1.500	0.30
Aspartame EP/USNF	2.500	0.50
Total	500.000	100.00

* signifies removed during lyophilisation process.

Example 7

[0060]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	425.000	85.00
Apomorphine HCl BP/EP	10.000	2.00
Domperidone	20.000	4.00
Gelatin EP/USNF	20.000	4.00
Mannitol EP/USP	15.000	3.00
Glycine USP	5.000	1.00
Aspartame EP/USNF	2.500	0.50
Peppermint Flavour	2.500	0.50
Total	500.000	100.00

* signifies removed during lyophilisation process.

Example 8

[0061]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	138.2500	92.1667
Lisuride Maleate	0.2000	0.1333
Gelatin EP/USNF	6.0000	4.0000
Mannitol EP/USNF	4.5000	3.0000
Aspartame EP/USNF	0.3000	0.2000
Cherry Flavour	0.7500	0.5000
Total	150.000	100.0000

* signifies removed during lyophilisation process.

Example 9

[0062]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	138.9500	92.6333
Pergolide Mesylate	0.2500	0.1667
Gelatin EP/USNF	6.0000	4.0000
Mannitol EP/USP	4.5000	3.0000
Aspartame EP/USNF	0.3000	0.2000
Total	150.0000	100.0000

* signifies removed during lyophilisation process.

Example 10

[0063]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	226.250	90.50
Bromocriptine Mesylate	2.500	1.00
Gelatin EP/USNF	10.000	4.00
Mannitol EP/USP	7.500	3.00
Aspartame EP/USNF	1.250	0.50
Cherry Flavour	1.250	0.50
Peppermint Flavour	1.250	0.50
Total	250.000	100.00

* signifies removed during lyophilisation process.

Example 11

[0064]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	137.750	91.8333
Ropinirole	1.000	0.6667
Gelatin EP/USNF	6.000	4.0000
Mannitol EP/USP	4.500	3.0000
Aspartame EP/USNF	0.750	0.5000
Total	150.000	100.0000

* signifies removed during lyophilisation process.

Example 12

[0065]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	431.500	86.30
Apomorphine HCl BP/EP	10.000	2.00
Naloxone HCl BP/EP	10.000	2.00
Gelatin EP/USNF	20.500	4.10
Mannitol EP/USP	15.000	3.00
Citric Acid EP/USP	1.500	0.30
Aspartame EP/USNF	3.000	0.60
Grapefruit Flavour	1.000	0.20
Glycine USP	7.500	1.50
Total	500.000	100.00

* signifies removed during lyophilisation process.

Example 13

[0066]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	413.000	82.60
Apomorphine HCl BP/EP	10.000	2.00
Naltrexone HCl	25.000	5.00
Gelatin EP/USNF	22.500	4.50
Mannitol EP/USP	15.000	3.00
Citric Acid EP/USP	2.500	0.50
Aspartame EP/USNF	5.000	1.00
Raspberry Flavour	2.000	0.40

* signifies removed during lyophilisation process.

(continued)

Ingredient	Parts by Weight	% by weight of composition
Glycine USP	5.000	1.00
Total	500.000	100.00

Example 14

[0067]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	397.250	79.45
Apomorphine HCl BP/EP	20.000	4.00
Naloxone HCl BP/EP	10.000	2.00
Domperidone	20.000	4.00
Gelatin EP/USNF	22.500	4.50
Mannitol EP/USP	17.500	3.50
Citric Acid EP/USP	1.500	0.30
Lemon Lime Flavour	2.500	0.50
Glycine USP	5.000	1.00
Aspartame EP/USNF	3.750	0.75
Total	500.000	100.00

* signifies removed during lyophilisation process.

Example 15

[0068]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	219.008	87.60
Apomorphine HCl BP/EP	5.000	2.00
Granisetron HCl	1.117	0.45
Gelatin EP/USNF	10.625	4.25
Mannitol EP/USP	7.500	3.00
Citric Acid EP/USP	1.500	0.60
Mint Flavour	1.500	0.60
Glycine USP	1.250	0.50
Aspartame EP/USNF	2.500	1.00
Total	250.000	100.00

* signifies removed during lyophilisation process.

Example 16

[0069]

Ingredient	Parts by Weight	% by weight of composition
Purified Water EP/USP*	416.0	83.2
Gelatin	18.0	3.6
Mannitol	13.5	2.7
Testosterone undecanoate	50.0	10.0
Aspartame	2.5	0.5
	500.00	100.0

* signifies removed during lyophilisation process.

Claims

1. The use of a pharmaceutical composition for oral administration comprising a carrier and active ingredient selected from a dopamine agonist, testosterone and mixtures thereof, the composition being in the form of a solid fast-dispersing dosage form which disintegrates within 1 to 60 seconds of being placed in the oral cavity for the manufacture of a medicament for treatment of male erectile dysfunction.

2. The use to claim 1 in which the composition is in the form of a solid fast-dispersing dosage form comprising a network of the active ingredient and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

3. The use according to claim 1 in which the composition comprises a dopamine agonist in an amount from 0.05 to 5mg.

4. The use according to any one of the preceding claims in which the dopamine agonist is apomorphine or a salt thereof.

5. The use according to any one of the preceding claims in which the composition comprises a dopamine agonist and further includes an anti-emetic.

6. The use according to claim 5 in which the anti-emetic is present in an amount of from 1 to 120mg.

7. The use according to claim 6 in which the anti-emetic is domperidone.

8. The use according to any one of claims 4 to 7 which further includes an opioid antagonist.

9. The use according to claim 8 in which the opioid antagonist is present in an amount of from 0.5 to 100mg.

10. The use as claimed in claim 1 in which the active ingredient comprises testosterone.

11. The use as claimed in claim 10 in which the testosterone is present in an amount of 10 to 100mg.

Patentansprüche

1. Verwendung einer pharmazeutischen Zusammensetzung zur oralen Verabreichung, aufweisend einen Träger und einen Wirkstoff, ausgewählt aus einem Dopamin-Agonisten, Testosteron und Mischungen davon, welche Zusammensetzung in Form einer festen, schnell dispergierenden Arzneimittel-Darreichungsform vorliegt, die innerhalb von 1 bis 60 Sekunden nach Einbringen in die Mundhöhle zerfällt; und zwar zur Herstellung eines Medikaments für die Behandlung der männlichen Erektionsstörung.

2. Verwendung nach Anspruch 1, bei der die Zusammensetzung in Form einer festen, schnell dispergierenden Arzneimittel-Darreichungsform vorliegt, aufweisend ein Netzwerk von Wirkstoff und einem wasserlöslichen oder wasserdispergierbaren Träger, der gegenüber dem Wirkstoff inert ist, wobei das Netzwerk durch Sublimieren von Lösemittel aus einer Zusammensetzung im festen Zustand erhalten wird, welche Zusammensetzung den Wirkstoff und eine Lösung des Trägers in einem Lösemittel aufweist.

3. Verwendung nach Anspruch 1, bei der die Zusammensetzung einen Dopamin-Agonisten in einer Menge von 0,05 bis 5 mg aufweist.

4. Verwendung nach einem der vorgenannten Ansprüche, bei der der Dopamin-Agonist Apomorphin oder ein Salz davon ist.

5. Verwendung nach einem der vorgenannten Ansprüche, bei der die Zusammensetzung einen Dopamin-Agonisten aufweist und ferner ein Antiemetikum einbezogen ist.

6. Verwendung nach Anspruch 5, bei der das Antiemetikum in einer Menge von 1 bis 120 mg vorliegt.

7. Verwendung nach Anspruch 6, bei der das Antiemetikum Domperidon ist.

8. Verwendung nach einem der vorgenannten Ansprüche, bei der ferner ein Opioid-Antagonist einbezogen ist.

9. Verwendung nach Anspruch 8, bei der der Opioid-Antagonist in einer Menge von 0,5 bis 100 mg vorliegt.

10. Verwendung nach Anspruch 1, bei der der Wirkstoff Testosteron ist.

11. Verwendung nach Anspruch 10, bei der das Testosteron in einer Menge von 10 bis 100 mg vorliegt.

Revendications

1. Utilisation d'une composition pharmaceutique pour l'administration orale, comprenant un véhicule et un ingrédient actif choisi parmi un agoniste de dopamine, la testostérone et des mélanges de ceux-ci, la composition étant sous la forme d'une forme de dosage solide à dispersion rapide qui se désintègre en l'espace de 1 à 60 secondes après avoir été placée dans la cavité buccale, pour la fabrication d'un médicament pour le traitement d'une dysérection mâle.

2. Utilisation selon la revendication 1, dans laquelle la composition est sous la forme d'une forme de dosage solide à dispersion rapide comprenant un réseau de l'ingrédient actif et un véhicule soluble ou dispersible dans l'eau qui est inerte vis-à-vis de l'ingrédient actif, le réseau ayant été obtenu en sublimant le solvant à partir d'une composition à l'état solide, cette composition comprenant l'ingrédient actif et une solution du véhicule dans un solvant.

3. Utilisation selon la revendication 1, dans laquelle la composition comprend un agoniste de dopamine en une quantité de 0,05 à 5 mg.

4. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle l'agoniste de dopamine est l'apomorphine ou un sel de celle-ci.

5. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la composition comprend un agoniste de dopamine et inclut en outre un anti-émétique.

6. Utilisation selon la revendication 5, dans laquelle l'anti-émétique est présent en une quantité de 1 à 120 mg.

7. Utilisation selon la revendication 6, dans laquelle l'anti-émétique est la dompéridone.

8. Utilisation selon l'une quelconque des revendications 4 à 7, qui inclut en outre un antagoniste d'opioïde.

9. Utilisation selon la revendication 8, dans laquelle l'antagoniste d'opioïde est présent en une quantité de 0,5 à 100 mg.

10. Utilisation selon la revendication 1, dans laquelle l'ingrédient actif comprend la testostérone.

11. Utilisation selon la revendication 10, dans laquelle la testostérone est présente en une quantité de 10 à 100 mg.

Figure 1

Plasma apomorphine (ng/mL)
0
1
2
3
4
5
6
7
Time (min)
0
30
60
90
120
150
180
210
240
270
300
330
360
Example 2 (10mg)
Example 1 (10mg)